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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,245	10/09/2001	Joseph Roberts	078728-0104	3976

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,245	ROBERTS ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 23-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,17-22 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 10/6/05.

Claims 42-46 were added as requested.

Claims 1-46 are pending in the Application.

Claims 1-13, 17-22, and 41-46 are under consideration in this Office Action. Claims 14-16 and 23-40 are withdrawn as being drawn to non-elected subject matter. Linking claims 1-6 and 17-19 are considered to the extent that they embrace the elected invention.

Rejections Withdrawn

The rejection of claims 1-13, 17-22, and 41 are rejected under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's amendment.

Claim Objections

Claim 44 is objected to. The word "and" should be deleted from immediately after step (e), and inserted immediately before "(g)". Also a semicolon should probably be inserted after the last instance of "therapeutic agent" in step (f), and step (g) should be indented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Chinol et al (British Journal of Cancer 78(2): 189-197, 1998).

Chinol taught a method of assaying the effects on immunogenicity, pharmacokinetics and biodistribution of biochemical modifications to the polypeptide streptavidin. Streptavidin (M_r 66 kDa) was modified with monomethoxypolyethyelene glycol (mPEG) to varying extents (mean values of 3, 7, or 15 mPEG chains per polypeptide (see Table 1 on page 192). Each modified polypeptide was administered to a group of 5-6 subjects on days 0, 10, 16, and 51 in an excipient comprising 10 mM phosphate buffer. Blood was drawn from each subject on days 10, 16, 23, and 76 and tested for anti-avidin reactivity by ELISA. See paragraph bridging columns 1 and 2 on page 190; page 192, column 2, first full paragraph; and page 194, column 1, second and third full paragraphs. Anti-avidin reactivity is a measure of the antigenicity of the modified avidins, which in turn is considered to be a biological activity as recited in the claims. Pharmacokinetics and tissue distribution of each modified avidin were also measured. Chinol concluded that avidin modified with 7 mPEG chains was most suitable for therapeutic applications. See abstract. Pertinent to claim 9, Chinol taught that avidin is used in cancer therapy. See abstract.

Thus Chinol anticipates the claims.

Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Deckert et al (Int. Journal of Cancer 87:382-390, 2000).

Deckert taught a method of assaying immunogenicity, pharmacokinetics and microdistribution of PEG-modified humanized A33 antibody. The A33 antibody is used to target colon cancer tumors. See title and abstract. A33 antibodies were modified with 5kDa or 20 kDa methoxy-PEG-succinimidyl-succinate and administered to groups of 5 mice each in weeks 0, 1, 2, and 3. Blood was drawn in weeks 5, 9, and 13, and anti A33 antibody binding activity was assayed in the serum. See paragraph bridging pages 384 and 385, and Fig. 3 on page 385. This is taken as an indirect measure of a biological activity (antigenicity) of the modified A33 antibodies. So, Deckert taught a method in which differently pegylated antibodies are administered to subjects, followed by booster doses, and measures of antigenicity.

Thus Deckert anticipates the claims.

Response to Arguments

Applicant's arguments filed 10/6/05 have been fully considered but they are not persuasive.

Applicant considers the Chinol reference at page 11 of the response. Applicant argues that Chinol does not disclose comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent. This is unpersuasive because Chinol measured immunogenicity of

the modified compound multiple times after multiple administrations. See paragraph bridging columns 1 and 2 on page 190; page 192, column 2, first full paragraph; and page 194, column 1, second and third full paragraphs. So, Chinol measured the same biological activity at several time points after several administrations of differently modified compounds. Note that the specification at paragraph 43 states "biological activity" means any cellular or physiological response or reaction that that agent causes, either directly or indirectly, and that the biological activity is not necessarily the same activity as the therapeutic benefit that the agent bestows upon the subject. As a result it is reasonable to interpret "biological activity" to embrace antigenicity.

Applicant points out that Chinol used an ELISA to determine the titer of antibodies produced against mPEG-modified avidins, and indicates that Chinol did not measure the biological activity of biotin binding by streptavidin. This is correct, but not evidence of non-obviousness. The rejected claims do not exclude immunogenicity from the genus of biological activities that can be measured, and so Chinol did measure a biological activity of the modified compound.

With regard to the Deckert reference, Applicant argues at pages 11 and 12 of the response that Deckert does not disclose comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent after the modified agents have been administered to a subject. This is not correct. Deckert measured antigenicity of differently modified A33 antibodies by detecting antibodies against them multiple times after multiple administrations of the

modified A33 antibodies to a subject. See paragraph bridging pages 384 and 385, and Fig. 3 on page 385.

Applicant argues that the extent of PEGylation was determined solely on

Applicant argues that the extent of pegylation to use was determined by in vitro studies measuring the acceptable loss of biological activity, and that in vivo studies were used only to find which modifications reduced immunogenicity. Applicant notes that the binding activity of A33 antibodies in vivo was not measured. These arguments are unpersuasive because immunogenicity is considered to be a biological activity, so in vivo studies *were* used to assess a biological activity of differently modified compounds.

For these reasons the rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez et al (Med. Pediatr. Oncol. 34(3): 200-205, 2000) in view of Graham et al (Bone Marrow Transplant (21(9): 879-885, 1998), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Alvarez disclosed a comparative study of the effects of pegylated asparaginase relative to those of native asparaginase. Patients were given at least two doses of

pegylated asparaginase. See Fig.1 on page 202. Pegylated asparaginase caused toxicity including nausea, vomiting and pancreatitis in greater than half of recipients being treated for ALL. Patients were monitored by sequential serum amylase and lipase determinations. See abstract.

Alvarez did not teach the comparison of two different types of pegylated asparaginase.

Graham disclosed a clinical trial of pegylated asparaginase in the treatment of acute lymphoblastic leukemia (ALL). Patients received between 1 and 12 doses of pegylated asparaginase. Patients were monitored for relapse throughout the course of treatment. This is considered to amount to an assay of biological activity of the drug. Most of the patients who received the drug developed toxicities which resulted in abbreviated courses of administration. Symptoms included nausea, vomiting, and pancreatitis. See abstract. Evaluations of toxicity are also considered to be measurements of biological activity.

Francis taught that pegylation of protein drugs can cause can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Francis also taught that bioactivity, stability, immunogenicity, and toxicity may be affected by the way in which a protein drug is pegylated. See abstract, and pages 2-4. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis taught that the appropriate pegylation method is generally

determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a pegylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

At the time the invention was made, pegylation of asparaginase was seen to have both advantages (increased half-life and reduced immunogenicity) and disadvantages (increased toxicity). It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a variety of differently pegylated versions of asparaginase, because Francis suggests that positive attributes of pegylated drugs can be maximized, while minimizing negative attributes, by determining the optimum pegylation conditions. See abstract. It would have been obvious to then compare and test the resulting pegylated forms of asparaginase to determine which drug was the best. It is clear that it was routine in the art to compare different forms of asparaginase in head to head studies in vivo as taught by Alvarez. It would have been similarly obvious to measure the effects of the drugs after each injection, as patients undergoing treatment for ALL, such as those in the Graham and Alvarez studies, are continuously monitored for disease progress. Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the optimization process suggested by Francis,

and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph.

Thus the invention as a whole was prima facie obvious.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 above, and further in view of Petersen et al (US Patent 6,531,122)

The teachings of Alvarez, Graham, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also teaches that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Petersen teaches that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because

these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Claims 8, 11, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 above, and further in view of Roberts et al (J. Gen. Virol. 72:299-305,1991).

The teachings of Alvarez, Graham, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from Pseudomonas.

Roberts teaches that glutaminase asparaginase from Pseudomonas can be used to treat retroviral disease by repeated administration, and that pegylation of the enzyme increases its half-life several fold. See abstract, and page 304, penultimate sentence of column 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Pseudomonas asparaginase glutaminase by pegylation. One would have been motivated to do so in order to increase its half-life in vivo and to decrease its immunogenicity, as taught by both Roberts and Francis. It would have been similarly obvious to optimize the pegylation conditions as taught by Francis. In doing so it would have been obvious to deliver differently pegylated forms of the enzyme in vivo over the course of treatment taught by Roberts. It would have been obvious to monitor the progress of the disease over the course of treatment in view of the teachings of Alvarez and Graham, who show that this is routine in the art.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 above, and further in view of Bollin et al (US Patent 4,678,812, issued 7/7/87).

The teachings of Alvarez, Graham, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient that protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the

purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 10/6/05 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections at pages 12-14 of the response. At page 13, Applicant argues that none of the cited references alone or in combination teach or suggest comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent. Applicant also notes that the objective of Alvarez was not to determine the extent of modification of asparaginase using differently modified enzymes, opines that Alvarez did not measure asparaginase activity, and states that the other cited references do not resolve these deficiencies. This is unpersuasive. The idea of comparing two drugs in *in vivo* studies is clearly not novel as Alvarez taught the comparison of pegylated and non-pegylated asparaginases. The biological activity measured by Alvarez was toxicity as indicated by nausea, vomiting, pancreatitis, and sequential serum amylase and lipase determinations. Note that the specification at paragraph 43 states "biological activity" means any cellular or physiological response or reaction that that agent causes, either directly or indirectly, and that the biological activity is not necessarily the same activity

as the therapeutic benefit that the agent bestows upon the subject. As a result it is reasonable to interpret "biological activity" to embrace any of toxicity, nausea, vomiting, pancreatitis, or amounts of serum amylase or lipase resulting form treatment. The assays of Alvarez were performed throughout the course of treatment which included several administrations of drug. It was clear from the teachings of Graham that the extent and conditions of pegylation were recognized in the art as variables that affect bioactivity, stability, immunogenicity, and toxicity, and that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See abstract; pages 2-4; and page 6, column 1, first full paragraph. Because Alvarez found that pegylation of asparaginase resulted in increased toxicity, and because Francis taught that drug toxicity could be differentially affected by the extent and conditions of pegylation, it clearly would have been obvious to perform studies similar to that of Alvarez in which two differently modified asparaginases were assayed.

At page 14, Applicant addresses the rejections as they might apply to new claims 42-46. Applicant's arguments in the first and third paragraphs of this section are addressed above. In the second paragraph Applicant argues essentially that the references do not teach or suggest comparing the selected biological activities of differently pegylated drugs to determine the relative bioavailability of the drugs, and selecting the type of biocompatible polymer, extent of modification, and conditions for modification based on relative bioavailability. This is unpersuasive because Francis taught that pegylation affects a variety of parameters including bioavailability (see page

2, column 1, item 5), and that the extent and conditions of drug pegylation can differentially affect the performance of the drug. As a result it would have been obvious to optimize pegylation conditions by taking into account effects on any of the parameters recognized as affected by pegylation, including bioavailability.

Applicant has asserted that none of the references suggests or discloses comparing the biological activity of differently modified therapeutic agents to select modification conditions that prevent host mediated inactivation. This is unpersuasive because it was well known in the prior art that host mediated inactivation of protein drugs was a problem that led to reduced circulation time and reduced effectiveness, and that one of the purposes of pegylation was to reduce host mediated inactivation. See e.g. Francis (1998) page 2, column 1, second full paragraph, and following items 1, 2, 4, 5, and 6. It is apparent that one purpose of the Francis article is to show that the type of pegylation used affects such factors as retention of bioactivity, stability, and immunogenicity. See abstract. Therefore, it was obvious that one of the purposes for comparing differently pegylated proteins was to select conditions that minimized host-mediated inactivation.

For these reasons, the rejections are considered proper and are maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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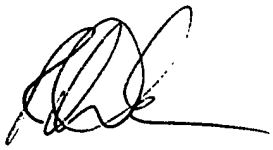

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